REMARKS

Claims 30, 71, 73-76, 85-89, and 91-115, are pending in the present application. Support for the amendments *supra* can be found throughout the specification and claims as filed, for example:

- Multi-epitopic antibody response: Example 1.
- Cytotoxic T cells: Example 2.
- Tumor-associated antigens and oncological diseases: CA125 (ovarian cancer cancer; Examples 1-2), CA15.3/MUC-1 (breast cancer; Example 5), CA19.9 (pancreatic, gastric, and colorectal cancers; Example 6), and prostate specific antigen (prostate cancer; Examples 7-9).
- Non-human antibodies – lines 1-10 of page 19.
- Shed antigens – see for example the discussion of soluble multi-epitopic tumor-associated antigens on page 18, and soluble antigens on pages 27-28.
- Dosages can be found, for example, in the section entitled "Dosage" beginning on page 22 and continuing through the Examples.
- "Circulating" antigen in new claim 115 can be found implicitly in the specification as filed as prostate specific antigen as described, for example on pages 18 and 27-28.

Applicant asserts that no new matter has been added by amendment. Issues raised in the Office Action will be addressed in the order they were raised by the Examiner. Applicants thank the Examiner for removing the finality of the rejections of Paper 14. Applicants also thank the Examiner for the interview of October 29, 2003, in which we discussed the invention, the rejections and cited art, and proposed claim amendments.

Applicants have amended the claims to recite stimulation of a multi-epitopic response to a tumor-associated antigen comprising administering a soluble complex of a tumor-associated antigen and antibody or antigen binding fragment that binds to a first epitope of the tumor-associated antigen, wherein the soluble complex induces host antibodies and/or cytotoxic T cells reactive with at least one other epitope of the antigen. Additional claims are directed to treating oncological diseases with the soluble complex.

Applicants further agreed to provide a specific discussion of the Klaus reference (*Nature* 272: 265-266 (1978)). Klaus teaches administration of an antibody-DNP complex and induction of anti-idiotype (Ab2) antibodies (see Figure 2). DNP is a small antigen that is not protein in nature and consists of a single epitope to which the antibody binds. At no point does Klaus teach or suggest the generation of antigen-specific antibodies via the anti-idiotypic network (Ab1 → Ab2 (anti-idiotype) → Ab3 (anti-anti-idiotype)), or via immune complex formation between an antibody and a multi-epitopic protein antigen.

Klaus further teaches that antibodies only acquire marked autoimmunogenicity when complexed with the eliciting antigen (see right column, page 266). This statement, as shown by Figure 2, relates only to induction of Ab2 antibodies which are immunoreactive with the administered antibody. At no point does Klaus teach or suggest that host antibodies and/or cytotoxic T cells reactive with other epitopes on a tumor-associated antigen (or any other antigen for that matter) could be induced in response to administration of a soluble complex of a tumor-associated protein antigen and an antibody or antigen-binding fragment as required by the current claims.

Claim Objections

1. Claims 74 and 92 are objected to because of an improper Markush group. Applicants have amended claims 74 and 92 to conform with the proper Markush format and respectfully request reconsideration and withdrawal of the rejection.

35 USC § 112, second paragraph

2. Claims 30, 71, 73-76, 88, 89, and 94 are rejected under 35 USC § 112, second paragraph as allegedly being indefinite.

Claim 30 has been amended to recite an "antibody" and "antigen binding fragment" rather than "Ab1"in an effort to further prosecution, however, Applicants assert that the term Ab1 is an art-recognized term in the anti-idiotypic network. Applicants assert that independent claim 30 and dependent claims 71 and 73-76 are now definite.

Applicants have amended claims 88 and 89 to recite the deposit information for antibodies B43.13 and AR20.5, and assert that the claims are now definite.

The mouse hybridoma AR20.5R8223, which makes the antibody Alt-1 (AR20.5), was deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, on, November 23, 1999, and was given ATCC deposit number PTA-975.

The mouse hybridoma B43.13, which makes the antibody Alt-2 (B43.13), was deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, on May 18, 2000, and was given ATCC deposit number PTA-1883.

Claim 85 has been amended such that the antigen and antibody/antigen binding fragment complex is soluble. Thus, claims 94 and 95 are now definite.

Applicants respectfully request reconsideration and withdrawal of the rejection.

35 USC 112, first paragraph

3. Claims 30, 71, 73-76, 85-87 and 91-97 were rejected under 35 U.S.C. § 112, first paragraph as allegedly containing new matter.

The Examiner stated that the claims were rejected for the recitation of "foreign mAb1 antibody". Applicants assert that there is support in the specification for a foreign mAb1 antibody as set forth in Example 1 wherein B43.13 is a mouse monoclonal Ab1 antibody administered to a human patient (i.e., foreign mAb1 antibody). Nevertheless, Applicants have amended the claims to recite "antibody" or "antigen-binding fragment" which are supported throughout the specification and the claims as filed. Applicants respectfully request reconsideration and withdrawal of the rejection.

4. Claims 30, 71, 73, 74, 76, 85-87, and 91-97 were rejected under 35 U.S.C. § 112, first paragraph as allegedly adequate written description.

The Examiner stated that the specification provides written description for two antibodies B43.13 and AR20.5 which bind to the human tumor antigens of CA125 and MUC-1 respectively, but not to any other antibody or antigen as broadly claimed.

The Federal Circuit recently handed down a decision declaring that Applicants have been unduly restricted in terms of written description by the fact-specific case of The Regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559, 1997 U.S. App. LEXIS 18221, 43 U.S.P.Q.2D (BNA) 1398 (Fed. Cir. 1997). Moba v. Diamond U.S. App. LEXIS 6285 (Fed. Cir. 2003). The Judge Rader rules that "the Lilly rule is not just a mere one-time mistake. It defies over thirty years of case law. It finds no scientific support in any statutory language. It creates a technology-specific rule in a technology neutral statute. It distorts the statute's rules for adequate disclosure of inventions. It complicates biotechnology patent drafting to the point of near impossibility and invites invalidating mistakes."

Applicants have amended the claims to recite "tumor-associated antigens" which have broad and explicit support throughout the Examples. Applicant has provided working examples of four tumor-associated antigens and oncological diseases: CA125 (ovarian cancer; Examples 1-2), CA15.3/MUC-1 (breast cancer; Example 5), CA19.9 (pancreatic, gastric, and colorectal cancers; Example 6), and prostate specific antigen (prostate cancer; Examples 7-9) with exemplary antibodies. Thus, Applicants have provided not only a description of what is encompassed by the current claims, but also working examples. One skilled in the art would recognize that each of these cancers is disparate in site and tumor-associated antigen and could be extrapolated to other tumor-associated antigens and human cancers. Applicants respectfully request reconsideration and withdrawal of the rejection.

Art rejections

5. Claims 85, 86, 91, 92, 94, 95, and 97 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Morgan et al. (U.S. Patent 4,879,225).

Morgan et al. teach a composition comprising an insoluble complex of an antigen and antibody wherein the complex is specifically treated with insolubilized protein A. Morgan et al. further specifically teach that the insolubility is what increases immunogenicity of the complex.

Applicants have amended the claims to recite a soluble complex of a tumor-associated antigen and an antibody or antigen binding complex which induces a multi-epitopic response.

Thus, Applicants assert that the Morgan et al. patent does not anticipate the currently amended claims and respectfully request reconsideration and withdrawal of the rejection.

6. Claims 30, 71, and 73-76 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Baum et al. (*Cancer* 1994, 73 (3 suppl): 1121-1125) as evidenced by Madiyalakan et al. (*Hybridoma* 1995, 14: 199-203).

The claims have been amended such that a soluble complex of a tumor-associated antigen and an antibody or antigen-binding fragment are administered, wherein host antibodies and/or cytotoxic T cells reactive with other epitopes of the tumor-associated antigen are elicited.

Baum et al. and Madiyalakan et al. teach administration of radiolabeled antibodies or antibody fragments. Neither Baum et al. nor Madiyalakan et al. teach or suggest administration of a soluble complex as claimed. Nor do they teach that a multi-epitopic response could be generated.

Thus, Applicants assert that the Baum et al. evidenced by Madiyalakan et al. do not anticipate the currently amended claims and respectfully request reconsideration and withdrawal of the rejection.

7. Claims 30, 71, and 73-76 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Wagner et al. (*Biotechnology Therapeutics* 1992, 3: 81-89) as evidenced by Madiyalakan et al. (*Hybridoma* 1995, 14: 199-203).

Wagner et al. teach administration of radiolabeled antibodies or antibody fragments. Madiyalakan et al. has been discussed *supra*. Neither Wagner et al. nor Madiyalakan et al. teach or suggest administration of a soluble complex as claimed. Nor do they teach that a multi-epitopic response could be generated.

Thus, Applicants assert that the Wagner et al. evidenced by Madiyalakan et al. do not anticipate the currently amended claims and respectfully request reconsideration and withdrawal of the rejection.

8. Claims 30, 71, and 73-75 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Diamandis et al. (U.S. Patent 6,068,830) as evidenced by Schwartz ("Cancer

Markers", In: Cancer: Principles and Practice of Clinical Oncology, 4th Edition, 1994, DeVita et al. Eds. Pages 531-542).

Diamandis et al. teach administration of an antibody immunoreactive with PSA.

Diamandis et al. do not teach or suggest administration of a soluble complex as claimed. Nor does it teach that a multi-epitopic response could be generated. Schwartz cannot compensate for the deficiencies of Diamandis et al.

Thus, Applicants assert that the Diamandis et al. evidenced by Schwartz et al. do not anticipate the currently amended claims and respectfully request reconsideration and withdrawal of the rejection.

9. Claims 30, 71, and 73-76 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Goldenberg et al. ("Cancer Diagnosis and Therapy with Radiolabeled Antibodies", In: Immunoconjugates, Antibody Conjugates and Radioimaging and Therapy of Cancer, Vogel, Ed., 1987, pages 259-280) as evidenced by Schwartz.

Goldenberg et al. teaches administration of a radiolabeled antibody. One skilled in the art would recognize that the radiolabel would be the cytotoxic agent. Goldenberg et al. do not teach or suggest administration of a soluble complex as claimed. Nor does it teach that a multi-epitopic response could be generated. Schwartz cannot compensate for the deficiencies of Goldenberg et al.

Thus, Applicants assert that the Goldenberg et al. evidenced by Schwartz et al. do not anticipate the currently amended claims and respectfully request reconsideration and withdrawal of the rejection.

10. Claims 30, 71, 73, 74, and 76 were rejected 35 U.S.C. § 102(b) as allegedly being anticipated by Courtenay-Luck (U.D. Patent 5,591,593). Claim 75 was rejected 35 U.S.C. § 102(e) as allegedly being anticipated by Courtenay-Luck (U.D. Patent 5,591,593).

Courtenay-Luck teaches administration of an antibody immunoreactive with mucins. Courtenay-Luck does not teach or suggest administration of a soluble complex as claimed. Nor does it teach that a multi-epitopic response could be generated.

Thus, Applicants assert that Courtenay-Luck does not anticipate the currently amended claims and respectfully request reconsideration and withdrawal of the rejection.

11. Claims 85, 86, 91, 92, 93, and 96 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Storkus et al. (U.S. Patent 6,077,519).

Storkus et al. teach a composition comprising a dendritic cell (binding agent) and peptide antigen). Storkus et al. do not teach or suggest administration of a soluble antigen-antibody complex as claimed. Nor does it teach that a multi-epitopic response could be generated.

Thus, Applicants assert that Storkus et al. do not anticipate the currently amended claims and respectfully request reconsideration and withdrawal of the rejection.

12. Claims 85-87, 91, 94, 95, and 96 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by St. Remy et al. (U.S. Patent 4,740,371).

St. Remy et al. teach an allergen and an antibody for the down-regulation of the IgE response against said antigen. Applicants have amended the claims to recite a soluble complex of a tumor-associated antigen and antibody or antigen binding fragment. Regardless, the claims as previously recited necessitated induction of an immune response, not down-regulation.

Thus, in either instance, Applicants assert that St. Remy et al. do not anticipate the currently amended claims and respectfully request reconsideration and withdrawal of the rejection.

13. Claims 85, 86, 91, 92, and 96 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Berzofsky et al. (WO 94/21287).

Berzofsky et al. teach a composition comprising a dendritic cell (binding agent) and peptide antigen). Berzofsky et al. do not teach or suggest administration of a soluble antigen-antibody complex as claimed. Nor does it teach that a multi-epitopic response could be generated.

Thus, Applicants assert that Berzofsky et al. do not anticipate the currently amended claims and respectfully request reconsideration and withdrawal of the rejection.

14. Claims 85, 86, 91-93, and 96 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Cheever et al. (U.D. Patent 5,869,445).

Cheever et al. teach a composition comprising a dendritic cell (binding agent) and peptide antigen). Cheever et al. do not teach or suggest administration of a soluble antigen-antibody complex as claimed. Nor does it teach that a multi-epitopic response could be generated.

Thus, Applicants assert that Cheever et al. do not anticipate the currently amended claims and respectfully request reconsideration and withdrawal of the rejection.

15. Claims 30, 71, 73-76, 85-88, and 91-97 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Madiyalakan et al. (Hybridoma 1995, 14: 199-203) in view of Klaus et al. (Nature 1978, 272: 265-266) and the abstract of Bachmann et al. (European Journal of Immunology, 1994, 24: 2567-2570).

The deficiencies of Madiyalakan et al. and Klaus et al. have been discussed *supra*. The abstract of Bachmann et al. cannot cure the deficiencies of Madiyalakan et al. and Klaus et al. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

16. Claims 30, 73-76, 85-88, and 91-97 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 10, and 14-37 of co-pending application 09/641,833 in view of Madiyalakan et al. (Hybridoma 1995, 14: 199-203) in view of Klaus et al. (Nature 1978, 272: 265-266) and the abstract of Bachmann et al. (European Journal of Immunology, 1994, 24: 2567-2570).

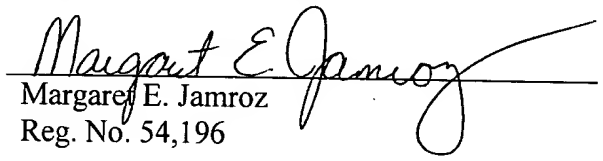
Applicants herewith provide a copy of the claims of co-pending application 09/641,833 as recently allowed (Appendix A). The deficiencies of Madiyalakan et al., Klaus et al., and Bachmann et al. have been discussed *supra*.

Applicants assert that the claims as currently recited are not obvious in view of the allowed claims of co-pending application 09/641,833 in view of any of the cited references and respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



Margaret E. Jamroz
Reg. No. 54,196

Date: November 26, 2003

Customer No: 28120
Docketing Specialist
Ropes & Gray, LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050